A Multicenter, Randomized, Double-Blind, Placebo-Controlled, 16-Week Study of Adjunctive Aripiprazole for Schizophrenia or Schizoaffective Disorder Inadequately Treated With Quetiapine or Risperidone Monotherapy

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Objective: Combining antipsychotics is common practice in the treatment of schizophrenia. This study investigated aripiprazole adjunctive to risperidone or quetiapine for treating schizophrenia and schizoaffective disorder.

Method: In this multicenter, double-blind, 16-week, placebo-controlled study conducted at 43 American sites from July 2006 to October 2007, patients with chronic, stable schizophrenia or schizoaffective disorder diagnosed with *DSM-IV-TR* were randomly assigned to receive aripiprazole (2–15 mg/d) or placebo in addition to a stable regimen of quetiapine (400–800 mg/d) or risperidone (4–8 mg/d). The primary outcome measure was the mean change from baseline to endpoint (week 16, last observation carried forward) in the Positive and Negative Syndrome Scale (PANSS) total score.

Results: 323 subjects being treated with either risperidone (n = 177) or quetiapine (n = 146) were randomly assigned to receive adjunctive aripiprazole (n = 168) or placebo (n = 155). Baseline characteristics were similar (mean PANSS total score: aripiprazole, 74.5; placebo, 75.9) except for history of suicide attempts (aripiprazole, 27%; placebo, 40%). Nearly 70% of subjects in each arm completed the trial. Adjunctive aripiprazole and placebo groups were similar in the mean change from baseline to endpoint in the PANSS total score (aripiprazole, −8.8; placebo, −8.9; $P = .942$). The incidence of treatment-emergent adverse events was similar between groups. Mean changes in Simpson-Angus Scale, Abnormal Involuntary Movement Scale, and Barnes Akathisia Rating Scale scores were not statistically significantly different. Adjunctive aripiprazole was associated with statistically significantly greater decreases in mean serum prolactin levels from baseline than was adjunctive placebo (−12.6 ng/mL for aripiprazole vs −2.2 ng/mL for placebo; $P < .001$), an effect that was seen in the risperidone subgroup (−18.7 ng/mL vs −1.9 ng/mL; $P < .001$) but not in the quetiapine subgroup (−3.01 ng/mL vs +0.15 ng/mL; $P = .104$).

Conclusions: The addition of aripiprazole to risperidone or quetiapine was not associated with improvement in psychiatric symptoms but was generally safe and well tolerated. Further research is warranted to explore whether antipsychotic combination therapy offers benefits to particular patient populations—for example, in cases of hyperprolactinemia.

Trial Registration: clinicaltrials.gov Identifier: NCT00325689

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Whereas combination therapy is standard practice in bipolar disorder[1] and necessary for difficult-to-treat major depressive disorder,[2] monotherapy is still consistently advocated in schizophrenia.[3–5] However, antipsychotic polypharmacy is common practice in schizophrenia treatment, with reported incidences from 13% to 90%.[6–10] Polypharmacy is often continued after cross-titration when symptom improvement is seen before the initial antipsychotic treatment is discontinued.

Although the benefits of antipsychotic polypharmacy have not been empirically established,[11,12] many clinicians resort to combinations to manage chronic, treatment-resistant illness and to alleviate or prevent the dose-dependent side effects.[13] With the increasing availability of pharmacologically novel antipsychotics, the likelihood of antipsychotic polypharmacy may also increase.

The rational use of polypharmacy has been hampered by the lack of systematic research due to difficulties in the

design and conduct of combination therapy trials.[14] Case studies and small trials have reported benefit with the addition of a second atypical antipsychotic to clozapine.[15–18] However, larger placebo-controlled or active-controlled studies of clozapine augmentation in nonresponsive or partially responsive patients have produced mixed results, with 1 positive trial of amisulpride augmentation[19] and both positive[20] and negative[21–23] trials with risperidone augmentation reported to date. Thus, further research is needed to establish fully any benefits of antipsychotic polypharmacy, especially for atypical antipsychotics with newer pharmacologic profiles, and for combinations that do not include clozapine, which by far predominate in clinical practice.

Aripiprazole is a second-generation antipsychotic that has been shown to be efficacious in patients with schizophrenia.[24–26] The rationale for using aripiprazole as an adjunctive agent relates to its distinct pharmacologic profile; aripiprazole has potent partial-agonist activity at the dopamine D_2 and D_3 receptors[27–29] and serotonin-1A ($5\text{-}HT_{1A}$)[30,31] receptors, as well as antagonism of $5\text{-}HT_2$ receptors.[32] Combining clozapine and aripiprazole was effective and tolerable in numerous case reports and open-label studies (see the Englisch and Zink review[33]). Furthermore, controlled trials have shown favorable improvement in negative symptoms[34] and significant benefits in weight and metabolic parameters.[35] Although other combinations are also justifiable, a rationale exists for adjunctive use of aripiprazole with risperidone or quetiapine. Aripiprazole has much higher affinity for D_2, $5\text{-}HT_{1A}$, and $5\text{-}HT_{2A}$ receptors than does quetiapine,[27,28] potentially increasing mesolimbic D_2 occupancy, thus increasing control of positive symptoms without the risk of histamine receptor H_1–related and muscarinic receptor M_1–related side effects that may limit higher quetiapine dosing, and improving depressive, cognitive, and negative symptoms. Adjunctive aripiprazole with risperidone may optimize D_2 receptor activity and hence diminish risk for extrapyramidal symptoms associated with risperidone[36] and decrease prolactin elevation resulting from high D_2 receptor occupancy by the full antagonist.[37] Thus, adjunctive aripiprazole may have potential benefits for efficacy and for amelioration of side effects that occur with monotherapy. To test this hypothesis, we undertook a controlled, prospective study to investigate the efficacy, safety, and tolerability of aripiprazole versus placebo as adjunctive therapy to a stable regimen of either risperidone or quetiapine monotherapy in patients with schizophrenia or schizoaffective disorder who did not fully respond to risperidone or quetiapine.

METHOD

Study Design

This was a randomized, double-blind, placebo-controlled, 16-week adjunctive therapy study consisting of a screening/washout phase (4–7 days), followed by a 16-week, double-blind treatment phase in which patients received either adjunctive aripiprazole or placebo with quetiapine or risperidone. Outpatients with chronic, stable schizophrenia or schizoaffective disorder, defined by the *DSM-IV-TR*,[38] who had an inadequate response to a stable dose of either quetiapine or risperidone, per investigator judgment, were enrolled. The trial was undertaken at 43 American sites from July 2006 to October 2007, and in accordance with the Declaration of Helsinki, the International Conference on Good Clinical Practice, and local regulatory requirements. Written informed consent was obtained from all patients.

Study Population

Outpatients of either gender, aged ≥ 18 years with chronic, stable schizophrenia or schizoaffective disorder and currently receiving a stable dose of quetiapine (400–800 mg/d) or risperidone (4–8 mg/d) for ≥ 4 weeks but with an inadequate response, were entered. To be considered stable, the patient must not have shown significant improvement or worsening of symptoms within 1 month of screening. Inadequate response was primarily defined by investigators' judgment as a Clinical Global Impressions-Severity of Illness scale (CGI-S)[39] score of 4 to 6, and patients had to have shown previous antipsychotic responsiveness (except with clozapine) in the past 12 months. Women of childbearing potential (not pregnant or breastfeeding) were permitted if they had a negative pregnancy test within 72 hours prestudy and were using contraception. Exclusion criteria included (1) a history of clozapine failure, (2) hospitalization due to their psychiatric illness in the past 3 months, (3) first episode of schizophrenia or schizoaffective disorder within the past year, (4) acute depression during the past month, (5) previous participation in a trial within the past month or any aripiprazole clinical trial, (6) suicidal ideation, (7) substance abuse/dependence, or (8) a history of seizure disorder. Patients were also ineligible if they had any medically significant abnormal laboratory test or vital sign or any medical condition that could interfere with assessments or expose them to unnecessary risk.

Dosing Schedule

Eligible patients must have received a stable dose of either quetiapine (400–800 mg/d) or risperidone (4–8 mg/d) for ≥ 4 weeks. Upon entry into the double-blind, dual-therapy phase, patients were stratified by current medication and randomly assigned to either adjunctive aripiprazole or placebo in a 1:1 ratio. Adjunctive aripiprazole was initiated at 5 mg/d with an option to decrease to a minimum of 2 mg/d (before week 2) if required for tolerability. By the end of week 2, an increase in dosage up to 10 mg/d was permitted, with a maximum of 15 mg/d allowed by the end of week 6. A 1-step reduction was allowed for tolerability between the end of weeks 2 and 8, and patients were subsequently discontinued if the lower dose was not tolerated. After the end of week 8, no dose changes were allowed. The target dose of aripiprazole was

10 mg/d (maximum, 15 mg/d). Concomitant medications, including the majority of antidepressants (only fluoxetine and paroxetine were not allowed); anticholinergics; mood stabilizers, including anticonvulsants (carbamazepine was not allowed); and benzodiazepines were permitted if patients had been receiving a regular dose for ≥ 4 weeks prior to study entry. New benzodiazepine use up to the maximum daily dose per package insert was permitted to manage treatment-emergent agitation or anxiety. Efficacy or safety rating-scale assessments were not conducted if benzodiazepines had been taken within 8 hours.

Assessments

The primary efficacy endpoint was the mean change from baseline to endpoint (week 16, last observation carried forward [LOCF]) in the Positive and Negative Syndrome Scale (PANSS)[40] total score. The key secondary endpoint was the mean change in the CGI-S score. Further secondary measurements were the mean change from baseline to endpoint in the scores of the following scales: the PANSS positive and negative subscales, the Calgary Depression Scale for Schizophrenia (CDSS),[41] the Arizona Sexual Experience Scale (ASEX),[42] the Fatigue Symptom Inventory (FSI),[43] the Brief Assessment of Cognition in Schizophrenia (BACS),[44] and the Subjective Well-Being under Neuroleptics (SWN)[45] scale. The mean scores at endpoint for the Clinical Global Impressions-Improvement scale (CGI-I)[39] and the Investigator's Assessment Questionnaire (IAQ)[46] total score were also assessed. The percentage of responders in each treatment group (defined as a decrease from baseline in PANSS total score ≥ 20% or a CGI-I score of 1 or 2) was also calculated. Assessments with the PANSS and CDSS were carried out on day 1 and weeks 2, 4, 8, 12, and 16 (or early termination point). The CGI-I assessment was conducted at weeks 2, 4, 6, 8, 12, and 16, while the CGI-S was also done at screening and day 1. The ASEX assessments were carried out on day 1 and week 16 or early termination point. The FSI was performed at day 1 and weeks 2, 6, 12, and 16. The SWN measurements were taken at day 1 and weeks 2, 8, and 16. The IAQ assessment was conducted at weeks 2, 4, 8, and 16.

Safety assessments included recording of adverse events (at day 1 and weeks 2, 4, 6, 8, 12, and 16 or early termination), physical examination (at screening and week 16 or early termination), measurements of vital signs (at screening, day 1, and weeks 2, 4, 6, 8, 12, and 16 or early termination), and laboratory tests (at screening and week 16 or early termination). Changes from baseline to week 16 in body weight, fasting glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, fasting triglycerides, and prolactin were monitored. Abnormal metabolic laboratory parameters were defined as follows: fasting glucose ≥ 100 mg/dL, total cholesterol ≥ 240 mg/dL, HDL cholesterol < 40 mg/dL, LDL cholesterol ≥ 160 mg/dL, and fasting triglycerides ≥ 150 mg/dL. The percentage of patients gaining ≥ 7% of baseline body weight was also assessed. The mean changes from baseline to week 16 for the Simpson-Angus Scale,[47] Abnormal Involuntary Movement Scale (AIMS),[48] and Barnes Akathisia Rating Scale (BARS)[49] scores were also measured. The Simpson-Angus Scale was measured at day 1 and weeks 4, 8, and 16; the AIMS was evaluated at day 1 and week 16; and the BARS was assessed at day 1 and weeks 2, 4, 8, and 16.

Analyses for efficacy and safety were also conducted for the quetiapine and risperidone subgroups, as well as for patients with schizophrenia only and schizoaffective disorder only.

Statistical Analysis

The sample size calculation was from nQuery Advisor, version 6.0 (STATCON, Witzenhausen, Germany), using the 2 means comparison method. It was anticipated that 338 patients would be randomly assigned and that 90% would be evaluable, 152 per arm, giving 90% power to differentiate between aripiprazole and placebo (plus atypical antipsychotic) when the true difference on the primary endpoint is 6, which assumes a standard deviation of 16 with a 2-sided *t* test at the level of .05 significance.

Safety summaries included all randomly assigned patients who took at least 1 treatment dose. The aripiprazole safety sample, however, included 1 patient randomly assigned to placebo who received aripiprazole. Efficacy analyses included all safety-sample patients who had at least 1 postrandomization efficacy evaluation. The LOCF data set was used for all analyses unless stated otherwise.

The primary endpoint—mean change from baseline to endpoint (week 16, LOCF) in the PANSS total score—was analyzed by analysis of covariance, with treatment as main effect, controlling for baseline PANSS total score, study center, and open-label medication status for the pooled data set (both quetiapine and risperidone open-label medication groups).

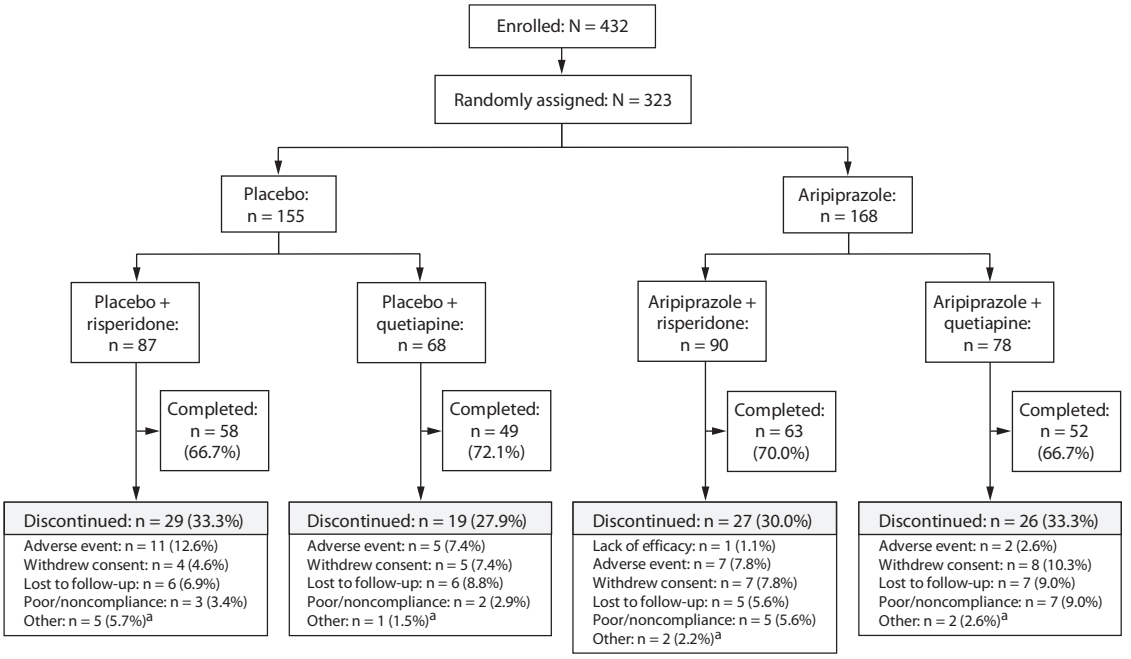
The mean changes in PANSS total score, CGI-S score, SWN score, total IAQ score, and safety endpoints that are continuous variables were analyzed using analysis of covariance or analysis of variance. Unless otherwise specified, categorical variables were analyzed by the Cochran-Mantel-Haenszel test. The time-to-event endpoints were analyzed using the log rank test to test the null hypothesis of identical survival function between 2 treatments. The *P* values for comparisons of aripiprazole and placebo were 2-tailed, using the 5% significance level.

RESULTS

Patient Disposition and Demographics

In total, 323 patients were randomly assigned to adjunctive aripiprazole (n = 168) or placebo (n = 155), and the distribution of patients currently receiving either

Figure 1. Patient Disposition Showing the Flow of Patients Throughout the Study



a"Other" includes patients who no longer met study criteria, patients discontinued due to administrative reasons of the sponsor, and patients discontinued for other reasons not specified.

quetiapine (n = 78 for aripiprazole vs n = 68 for placebo) or risperidone (n = 90 for aripiprazole vs n = 87 for placebo) was similar (Figure 1). Completion rates were similar, with 68.5% of aripiprazole-treated patients (n = 115) and 69.0% of placebo-treated patients (n = 107) remaining at week 16. There was no difference in the time to discontinuation between adjunctive aripiprazole and placebo (hazard ratio [HR] = 1.01; $P = .948$), irrespective of whether the initial antipsychotic was quetiapine or risperidone. The reasons for study discontinuation were the following (adjunctive aripiprazole vs placebo): adverse event (5.4% vs 10.3%); subject withdrew consent (8.9% vs 5.8%); subject was lost to follow-up (7.1% vs 7.7%); poor/noncompliance (7.1% vs 3.2%); other reasons (2.4% vs 3.9%); and lack of efficacy (0.6% vs 0%) (Figure 1).

Patient demographics are displayed in Table 1. Overall, the mean age was 44 years, and the majority of the population were male (61.3%), black/African American (53.3%), and diagnosed with schizophrenia (78.0%). The mean PANSS total score at baseline was 75.

At baseline, the percentage of patients with abnormal metabolic laboratory parameters was high—and similar between aripiprazole and placebo (fasting total cholesterol, 7.7% vs 7.8%; HDL cholesterol, 32.5% vs 22.2%; fasting triglycerides, 26.6% vs 28.1%; fasting glucose, 25.4% vs 26.8%; LDL cholesterol, 7.7% vs 6.5%; safety sample). Baseline mean body mass index (BMI [kg/m^2]) values were similar between groups (aripiprazole, 31.8 vs placebo, 31.1), and a similar proportion of patients in each group had BMI values in the overweight (BMI 25–30: aripiprazole, 31.7% vs placebo, 25.2%) or obese (BMI ≥ 30: aripiprazole, 48.8% vs placebo, 50.3%) categories at baseline (efficacy sample). Similar baseline values were seen in the atypical antipsychotic subgroups.

Treatment and Dosing

The mean dose of aripiprazole at endpoint was 10.3 mg/d and was similar between those receiving adjunctive quetiapine (10.2 mg/d) and risperidone (10.4 mg/d). The mean dose of quetiapine at endpoint was 516 mg/d and 513 mg/d for the placebo and aripiprazole arms, respectively. The mean dose of risperidone at endpoint was 4.8 mg/d and 4.6 mg/d for the placebo and aripiprazole arms, respectively. Mean doses of both quetiapine and risperidone are consistent with the current recommendations in the product labels.

Efficacy Outcome

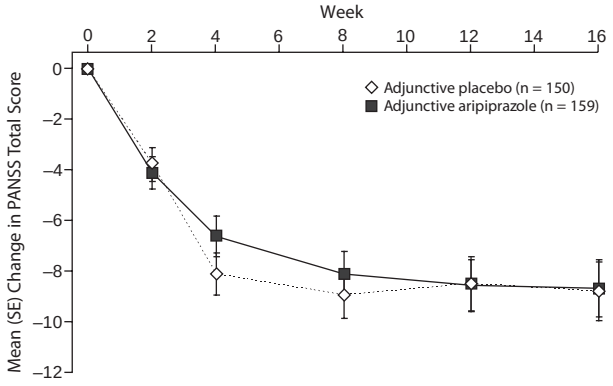
There was no difference in the mean change from baseline to week 16 in PANSS total score between the adjunctive aripiprazole and placebo groups (–8.8 vs –8.9; $F_{1,269} = 0.01$, $P = .942$; LOCF) (Figure 2). When we compared the data by antipsychotic subgroup (quetiapine or risperidone), no significant differences were seen in the change of PANSS total score at week 16 between aripiprazole and placebo.

Table 1. Patient Demographics and Characteristics at Baseline—Randomized Sample

Characteristic	Placebo (n = 155)	Aripiprazole (n = 168)	Total (N = 323)
Age, mean (SD), y	44.4 (12.0)	44.1 (11.3)	44.2 (11.6)
Gender, n (%)			
Male	99 (63.9)	99 (58.9)	198 (61.3)
Female	56 (36.1)	69 (41.1)	125 (38.7)
Race, n (%)			
White	72 (46.5)	70 (41.7)	142 (44.0)
Black/African American	79 (51.0)	93 (55.4)	172 (53.3)
Asian	2 (1.3)	2 (1.2)	4 (1.2)
American Indian/ Alaska native	0	1 (0.6)	1 (0.3)
Native Hawaiian/ other Pacific Islander	1 (0.6)	2 (1.2)	3 (0.9)
Other	1 (0.6)	0	1 (0.3)
Weight, mean (SD), kg	92.0 (22.4)	92.7 (22.8)	92.3 (22.5)
DSM-IV-TR classification, n (%)			
Schizophrenia	122 (78.7)	130 (77.4)	252 (78.0)
Schizoaffective disorder	33 (21.3)	38 (22.6)	71 (22.0)
Schizophrenia type, n (%)			
Disorganized	0	1 (0.8)	1 (0.4)
Paranoid	110 (90.2)	112 (86.2)	222 (88.1)
Residual	1 (0.8)	2 (1.5)	3 (1.2)
Undifferentiated	11 (9.0)	15 (11.5)	26 (10.3)
PANSS total score, mean (SD)[a]	75.9 (13.0)	74.5 (13.3)	75.2 (13.2)

[a]Cronbach α of PANSS total score is 0.83.
Abbreviations: *DSM-IV-TR* = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision; PANSS = Positive and Negative Syndrome Scale.

Figure 2. Mean Change From Baseline to Week 16 in PANSS Total Scores (LOCF)—Efficacy Sample[a]



[a]Baseline mean (SE) PANSS total scores: adjunctive placebo, 75.9 (1.0); adjunctive aripiprazole, 74.3 (1.0).
Abbreviations: LOCF = last observation carried forward, PANSS = Positive and Negative Syndrome Scale.

Table 2 summarizes the secondary efficacy results. There were no significant between-group differences in mean change from baseline in CGI-S scores, PANSS positive or negative scores, SWN scores, or mean CGI-I score. Both groups showed improvements in CDSS scores, although the difference between groups was not significant. Response rates were also similar between treatments (aripiprazole,

Table 2. Summary of Secondary Outcome Measurements—Efficacy Sample

Outcome Measure	Placebo (n = 150)	Aripiprazole (n = 160)	Treatment Comparison: Aripiprazole vs Placebo		
			F or χ^2	*df*	*P*
CGI-S score					
Mean at baseline	4.2	4.2			
Mean change from baseline	−0.5	−0.5	$F = 0.16$	1,270	.689
PANSS positive score					
Mean at baseline	19.3	19.6			
Mean change from baseline	−3.1	−2.6	$F = 1.18$	1,269	.279
PANSS negative score					
Mean at baseline	20.0	19.0			
Mean change from baseline	−1.9	−1.8	$F = 0.04$	1,269	.836
Mean CGI-I score at endpoint	3.2	3.1	$F = 0.37$	1,271	.545
CDSS score					
Mean at baseline	4.7	4.0			
Mean change from baseline	−1.2	−1.2	$F = 0.01$	1,269	.927
SWN score					
Mean at baseline	79.7	82.0			
Mean change from baseline	1.9	0.8	$F = 0.53$	1,269	.466
Response rate, %[a]	40.7	41.3	$\chi^2 = 0.053$	1	.818

[a]Response = ≥20% decrease from baseline in PANSS total score or a CGI-I score of 1 or 2.
Abbreviations: CDSS = Calgary Depression Scale for Schizophrenia, CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, PANSS = Positive and Negative Syndrome Scale, SWN = Subjective Well-Being Under Neuroleptics scale.

41.3% vs placebo, 40.7%; $\chi^2_1 = 0.053$, $P = .818$), as were mean IAQ scores at study endpoint (aripiprazole, 27.2 vs placebo, 27.5; $F_{1,170} = 0.36$, $P = .55$).

There was no difference in the mean change from baseline to week 16 in ASEX total scores between adjunctive aripiprazole and placebo groups (0.2 vs −0.4; $F_{1,212} = 1.20$, $P = .275$; observed cases). Both groups experienced similar mean improvement from baseline in FSI items using the "most fatigued days" scales (aripiprazole, −0.6 vs placebo, −0.6; $F_{1,269} = 0.05$, $P = .819$; LOCF) and FSI interference total score (aripiprazole, −1.4 vs placebo, −2.2; $F_{1,269} = 0.21$, $P = .650$; LOCF). Mean changes from baseline to week 16 in the BACS *Z*-score (calculated from BACS standardized composite score) and individual subtests are shown in Table 3 for the total population and by antipsychotic subgroup (quetiapine or risperidone). There were no significant differences between the adjunctive aripiprazole and placebo groups in either *Z*-scores or individual test scores for either the total population or individual atypical subgroups.

Subgroup analysis revealed that improvement in mean PANSS total scores with aripiprazole versus placebo was greater in patients with schizoaffective disorder (−13.6 vs −8.1; treatment difference, −5.5; $P = .145$) than in those with schizophrenia (−7.3 vs −8.5; treatment difference, 1.2; $P = .505$), although not statistically significant.

Table 3. Mean (SE) Change From Baseline in Brief Assessment of Cognition in Schizophrenia (BACS) Composite and Individual Scores—Observed-Case Dataset, Efficacy Sample

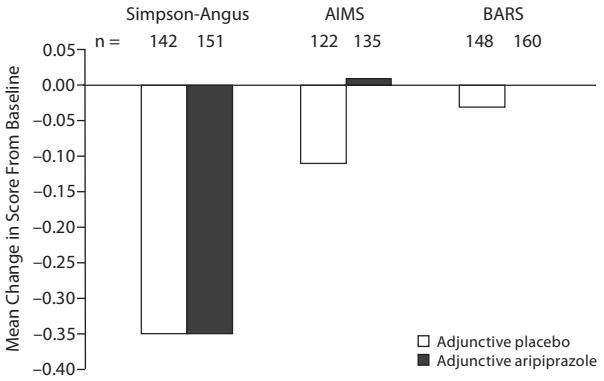
	Total Population		Risperidone Subgroup		Quetiapine Subgroup	
BACS Subtest	Placebo (n = 118)	Aripiprazole (n = 126)	Placebo (n = 64)	Aripiprazole (n = 71)	Placebo (n = 54)	Aripiprazole (n = 55)
BACS *Z*-score[a,b]	0.13 (0.61)	0.10 (0.63)	0.20 (0.59)	0.14 (0.59)	0.06 (0.63)	0.05 (0.68)
Verbal memory score	−0.07 (0.92)	0.06 (1.01)	0.03 (0.98)	0.10 (1.00)	−0.18 (0.84)	0.02 (1.03)
Digit sequencing score	0.10 (0.55)	0.02 (0.66)	0.15 (0.53)	0.03 (0.73)	0.04 (0.58)	0.01 (0.55)
Token motor task score[c]	0.13 (1.16)	0.10 (0.04)	0.16 (1.12)	0.14 (0.95)	0.09 (1.22)	0.04 (1.15)
Verbal fluency score[d]	0.08 (0.67)	−0.01 (0.70)	0.07 (0.65)	0.04 (0.63)	0.09 (0.69)	−0.07 (0.77)
Symbol coding score[e]	0.03 (0.50)	0.06 (0.64)	0.10 (0.49)	0.07 (0.46)	−0.05 (0.50)	0.04 (0.82)
Tower of London score[f]	0.39 (1.32)	0.19 (1.20)	0.48 (1.17)	0.20 (1.32)	0.29 (1.48)	0.18 (1.03)

[a]BACS *Z*-score was calculated from BACS standardized composite score, which was derived from 6 standardized subscale scores.
[b]Total population: placebo n = 117; risperidone subgroup: placebo n = 63.
[c]Total population: placebo n = 115, aripiprazole n = 124; risperidone subgroup: placebo n = 62; quetiapine subgroup: placebo n = 53, aripiprazole n = 53.
[d]Total population: placebo n = 117, aripiprazole n = 124; risperidone subgroup: placebo n = 63, aripiprazole n = 69.
[e]Total population: placebo n = 116, aripiprazole n = 125; risperidone subgroup: placebo n = 62, aripiprazole n = 70.
[f]Total population: placebo n = 117, aripiprazole n = 125; risperidone subgroup: placebo n = 63; quetiapine subgroup: aripiprazole n = 54.

Table 4. Adverse Events Occurring With an Incidence of ≥ 5% in Either Group—Safety Sample (total N = 322)

Adverse Event	Placebo (n = 153), n (%)	Aripiprazole (n = 169), n (%)
Fatigue	10 (6.5)	14 (8.3)
Headache	13 (8.5)	12 (7.1)
Insomnia	13 (8.5)	11 (6.5)
Akathisia	11 (7.2)	10 (5.9)
Somnolence	7 (4.6)	10 (5.9)
Psychotic disorder	9 (5.9)	1 (0.6)
Back pain	4 (2.6)	10 (5.9)

Figure 3. Mean Change From Baseline to Week 16 in AIMS Scores, Simpson-Angus Scale Total Scores, and BARS Akathisia Global Clinical Assessment Scores (LOCF)—Safety Sample



Abbreviations: AIMS = Abnormal Involuntary Movement Scale, BARS = Barnes Akathisia Rating Scale, LOCF = last observation carried forward.

Table 5. Median Change in Metabolic Parameters From Baseline to Week 16 (LOCF) by Treatment Group[a]

Metabolic Parameter (mg/dL)	Placebo	Aripiprazole	*P* Value
Fasting glucose[b]			
Baseline	95.0	92.0	
Week 16	2.0	2.5	.851
LDL cholesterol[c]			
Baseline	114.0	108.0	
Week 16	0.0	−1.0	.455
Total cholesterol[d]			
Baseline	193.0	185.5	
Week 16	0.0	−2.0	.224
Fasting triglycerides[b]			
Baseline	126.0	126.0	
Week 16	−2.0	−16.0	.114
HDL cholesterol[d]			
Baseline	48.0	46.0	
Week 16	−2.0	0.0	.256

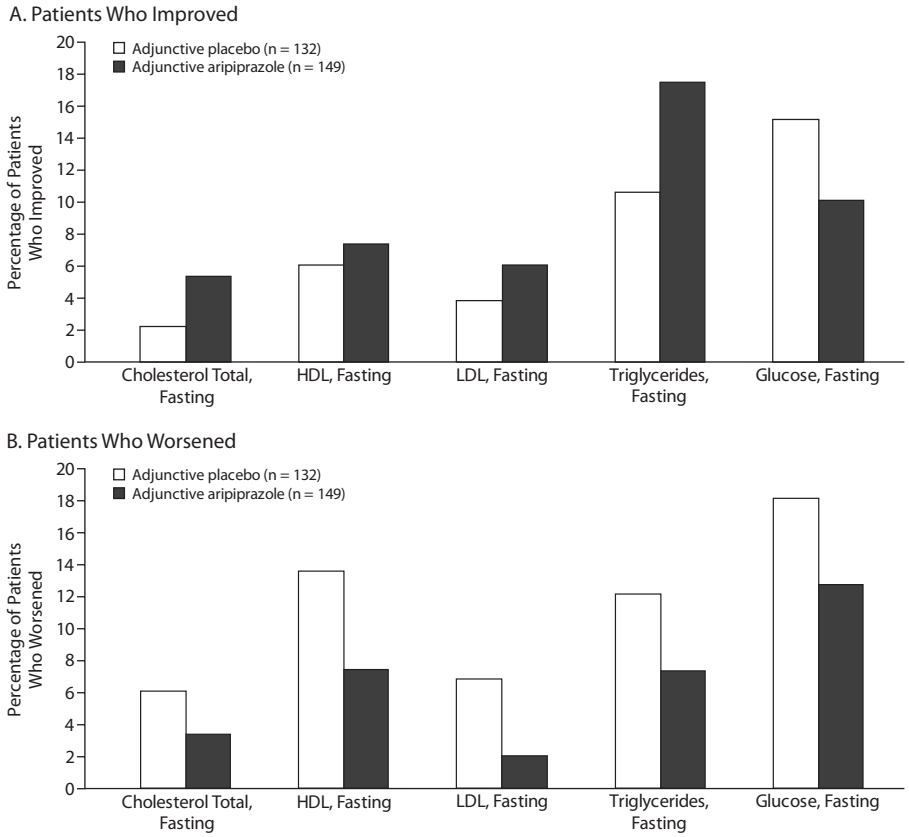
[a]Actual mean values are shown for baseline.
[b]Placebo: n = 89; aripiprazole: n = 86.
[c]Placebo: n = 121; aripiprazole: n = 131.
[d]Placebo: n = 121; aripiprazole: n = 132.
Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein, LOCF = last observation carried forward.

Safety and Metabolic Parameters

Adverse events occurring in ≥ 5% of either the adjunctive aripiprazole or placebo group are displayed in Table 4. The 3 most common adverse events with adjunctive aripiprazole were fatigue (8.3%), headache (7.1%), and insomnia (6.5%), and the 3 most common with adjunctive placebo were headache (8.5%), insomnia (8.5%), and akathisia (7.2%). Fewer patients had serious treatment-emergent adverse events with adjunctive aripiprazole than with placebo (4.7% vs 12.4%). The most frequently reported serious adverse events were psychiatric disorders (aripiprazole, n = 2 [1.2%]; placebo, n = 15 [9.8%]): in the aripiprazole group, these were 1 case of agitation and 1 of psychotic disorder; in the placebo group, there were 7 reports of psychotic disorder, 5 reports of suicidal ideation, and 1 report each for depression, hallucinations, homicidal ideation, paranoia, self-injurious behavior, and suicide attempt. No deaths were reported.

Extrapyramidal symptom–related events were reported by 8.3% of adjunctive aripiprazole–treated and 12.4% of adjunctive placebo–treated patients. Akathisia was reported in 5.9% of adjunctive aripiprazole–treated and 7.2% of adjunctive placebo–treated patients. Minimal, nonsignificant changes from baseline to endpoint in the AIMS total score and the BARS akathisia global clinical assessment were seen with adjunctive aripiprazole and placebo (Figure 3).

Figure 4. Percentage of Patients With (A) Abnormal Laboratory Parameters at Baseline and Normal Laboratory Parameters at Week 16, ie, Patients Who Improved, and (B) Normal Laboratory Parameters at Baseline With Abnormal Laboratory Parameters at Week 16, ie, Patients Who Worsened[a]



[a]Abnormal laboratory parameters were defined as follows: fasting glucose, ≥ 100 mg/dL; total cholesterol, ≥ 240 mg/dL; HDL cholesterol, < 40 mg/dL; LDL cholesterol, ≥ 160 mg/dL; triglycerides, ≥ 150 mg/dL.
Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein.

There was also no difference in the mean decreases in the Simpson-Angus total scores between adjunctive aripiprazole and placebo (Figure 3).

There were no significant differences in median changes from baseline to week 16 in fasting glucose, total cholesterol, fasting triglycerides, LDL cholesterol, or HDL cholesterol between treatment groups (Table 5). Most patients in both treatment groups experienced no change in metabolic parameters during 16 weeks of treatment (aripiprazole vs placebo: fasting total cholesterol, 91.3% vs 91.7%; HDL cholesterol, 85.2% vs 80.3%; LDL cholesterol, 92.0% vs 89.4%; fasting triglycerides, 75.2% vs 77.3%; fasting glucose, 77.2% vs 66.7%). The percentage of patients experiencing improvement (abnormal at baseline and normal at week 16) or worsening (normal at baseline and abnormal at week 16) of metabolic parameters during treatment is shown in Figure 4A and 4B, respectively.

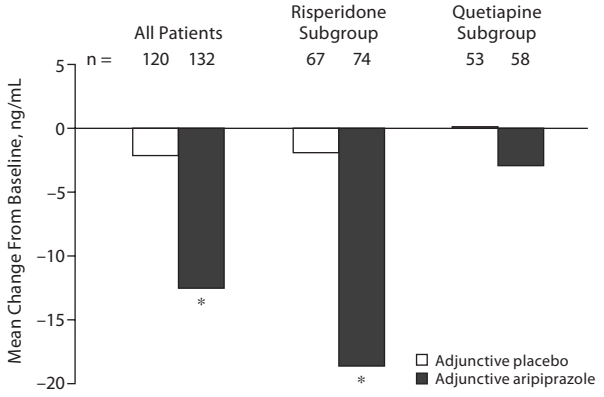
Mean weight change was similar between subjects receiving adjunctive aripiprazole and adjunctive placebo (1.3 kg vs 1.1 kg, respectively; $P = .728$); clinically relevant weight gain (≥ 7% gain from baseline) was observed at any time in 13.4% of patients in the adjunctive aripiprazole group and in 9.9% of patients in the adjunctive placebo group ($P = .445$).

Analysis of mean serum prolactin levels showed that adjunctive aripiprazole was associated with a statistically significant decrease from baseline in serum prolactin levels in comparison with adjunctive placebo (–12.6 ng/mL vs –2.2 ng/mL; $P < .001$; LOCF) (Figure 5). Subgroup analysis showed that mean serum prolactin levels were also significantly decreased with adjunctive aripiprazole compared to adjunctive placebo in the risperidone subgroup (–18.7 ng/mL vs –1.9 ng/mL; $P < .001$) but not in the quetiapine subgroup (–3.01 ng/mL vs + 0.15 ng/mL; $P = .104$) at endpoint. More adjunctive aripiprazole patients than adjunctive placebo patients with abnormal prolactin levels at baseline had normal prolactin levels at week 16 (19.5% vs 9.1%).

DISCUSSION

In this multicenter, randomized, double-blind, placebo-controlled trial, the addition of aripiprazole to either quetiapine or risperidone was not associated with a greater

Figure 5. Mean Change From Baseline to Week 16 in Serum Prolactin Levels in the Whole Study Population and in the Subgroups of Patients Who Received Placebo or Aripiprazole Adjunctive to Risperidone or Quetiapine (LOCF)—Safety Sample



*$P < .001$ vs placebo.
Abbreviation: LOCF = last observation carried forward.

improvement in schizophrenia symptoms, as measured by PANSS total score, versus placebo. Patients in both groups had a similar decrease in PANSS scores; the majority of improvement occurred during the first 4 weeks, with a subsequent plateau from weeks 8 to 16. Decreases in the PANSS were moderate but should be considered in the context of the relatively low mean baseline score of 75. The changes in secondary outcome measures were also comparable between groups. Aripiprazole added to quetiapine or risperidone was not associated with worsening of schizophrenia symptoms; in fact, there were 7 cases of psychosis exacerbation with antipsychotic monotherapy versus only 1 case with aripiprazole adjunctive to risperidone or quetiapine.

In general, aripiprazole added to quetiapine or risperidone was not associated with increases in side effects (including akathisia). There was a greater decrease in prolactin levels with aripiprazole than with placebo, driven by the decreases in the risperidone subgroup. Similar reductions in prolactin levels were seen following adjunctive use of aripiprazole in haloperidol-treated patients with hyperprolactinemia.[37] Importantly, there was no worsening of metabolic parameters following the addition of aripiprazole, and potential improvements are possible and warrant further investigation. Physical health issues are of high clinical relevance due to their associated cardiovascular morbidity and mortality, which improve following reduction of lipid levels.[50] Previous studies have shown some beneficial effects on lipid levels in aripiprazole augmentation of clozapine.[34,35,51]

This study is the largest double-blind, placebo-controlled, randomized study to date evaluating the effects of combining 2 atypical antipsychotics. It has addressed a key research question in schizophrenia—namely, the value of antipsychotic polypharmacy as a therapeutic strategy. Although this strategy is common in clinical practice, few studies with rigorous design have evaluated the outcomes of antipsychotic polypharmacy; the majority of studies undertaken used very small patient populations and produced conflicting data.[12,15–18,20–22]

Despite a prospective, randomized design, some methodological issues may have impacted the results; specifically, there was no requirement for a minimum baseline PANSS total score. Thus, the potential existed to enroll patients who were mildly symptomatic and not reflective of the patients who would most need combination therapy in real-life practice. Additionally, the lack of a prospective treatment phase to assess response to either quetiapine or risperidone means that we cannot be certain of the stability of patients' symptoms, treatment compliance, or adequate duration of treatment before entering the study.

Patients entering randomized treatment may not have been truly nonresponsive to previous medication. This possibility is supported by the large improvement in the adjunctive placebo group, which suggests that patients entering the study may not have been on a stable dose of their current antipsychotic long enough to have exhausted the benefits of the initial antipsychotic. It is also possible that some degree of expectancy bias influenced the ratings. Finally, the aripiprazole doses used may have been too low. If so, this may have had a major impact on efficacy; however, it is unclear whether increased doses of aripiprazole would have resulted in a switching effect.

CONCLUSION

This study failed to demonstrate that augmentation with aripiprazole 2–15 mg/d offers statistically significant improvement in psychiatric symptoms compared with placebo in patients with schizophrenia showing suboptimal response to quetiapine or risperidone monotherapy. However, aripiprazole augmentation was generally well tolerated. Adjunctive aripiprazole therapy may be beneficial for some patients by decreasing prolactin or triglycerides, although these findings need to be corroborated. Further studies to help elucidate the potential benefits and risks of various antipsychotic and nonantipsychotic augmentation strategies are needed. Subsequent studies should carefully establish the parameters of prior monotherapy treatment and response to maximize power to detect effects of the augmenting agent.

Drug names: aripiprazole (Abilify), carbamazepine (Carbatrol, Equetro, and others), clozapine (FazaClo, Clozaril, and others), fluoxetine (Prozac and others), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel), risperidone (Risperdal and others).

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